Sub E2 55. (New) The method of claim 55, ~~wherein said composition~~ comprises from about 10^8 to about ~~10^{11}~~ adenovirus particles. --

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REMARKS

I. Status of the Claims

Claims 1, 4, 5, 8, 10-15, 18-28 and 33-50 are pending in the application. Claims 1, 4, 5, 8, 10-12, 28 and 34-39 stand rejected under 35 U.S.C. §112, second paragraph, and all claims stand rejected under 35 U.S.C. §112, first paragraph. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejections Under 35 U.S.C. §112, Second Paragraph

The examiner has rejected claims 1 and 34 for reciting "the response" of a tumor cell. Applicants traverse, but in the interest of advancing the prosecution, have canceled these claims, rendering the rejection moot.

Claim 28 is rejected as reciting "adenovirus" but depending from a claim that recites herpesvirus. Applicants have canceled this claim, rendering the rejection moot.

III. Rejection Under 35 U.S.C. §112, First Paragraph

The examiner has maintained the rejection under §112, first paragraph, arguing that the specification does not teach certain key aspects of the invention and that the claims are overbroad. Each of these points is addressed below.

First, the examiner objects to the breadth of the term "response" in claims 1 and 34. Both of these claims have been canceled, thereby rendering the rejection moot.

Second, it is argued that the present invention is a form of "gene therapy" and, hence, has a high degree of unpredictability. However, applicants submit that the present invention merely relies on the infection of target cells by a virus. The subsequent expression of viral gene products results, as a matter of course, from the infection. No particular gene need be expressed, and no therapeutic gene need be provided at a given level or for a given duration. Thus, the characterization of this invention as "gene therapy" is not entirely correct and, to the extent that transgene expression is considered to be problematic, is misleading. The straightforward nature in which viruses are employed, according to the present invention, belies most, if not all, of the concerns surrounding "gene therapy." Thus, it is submitted that the examiner's comments are off the mark.

The examiner has again raised the issue of methods and routes of administration. Again, it should be noted that each of the independent claims recites that the herpesvirus is either contacted with the tumor cells or delivered to the tumor or tumor site. Thus, the claim itself, while not limiting the specific ***manner*** in which this occurs, contains an assurance that the herpesvirus reaches its target. Those of skill in the art are more than able to determine, depending on the given type or location of the tumor, the precise mode of administration. Moreover, the examiner has provided nothing in the way of evidence that would suggest that

specific routes and methods of administration are critical to the present invention, which merely involves the administration of infectious viral particles to a patient.

Next, the examiner argues that the scope of the claims is excessive, given that the claims are not restricted to HSV-1 and adenovirus type 5. The examiner merely speculates that the differences between respective herpesviruses and respective adenoviruses preclude any predictability in the ability to, in combination with radiotherapy, inhibit the growth of a tumor cell. In the interest of advancing the prosecution, applicants have amended the herpesvirus claims to recite HSV. The similarities between HSV-1 and HSV-2 overwhelm the differences, both from structural and functional standpoints. The record is devoid of any reason why one would suspect that these viruses would ***not*** provide the same effect, in combination with radiotherapy.

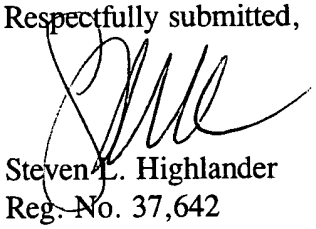
As for adenoviruses, there similarly is no basis of record for belief that differing the serotype of adenovirus from type 5, as exemplified, to any of the other types, would effect a different result according to the present invention. Rather, the examiner merely has alleged that the viruses differ in structure and activity to the point where predictability is lost. This kind of unsupported allegation cannot suffice to shift the burden back to applicants to ***prove*** the enabling quality of their disclosure. *In re Marzocchi*, 169 UPSQ 370 (CCPA 1971). The examiner has, therefore, failed to make out a *prima facie* case of non-enablement. Further, applicants submit that those of skill in the art would not doubt that the results with Ad5 would be representative of the results with other adenoviruses.

It is respectfully submitted, therefore, that the rejections, on all bases, are improper. Reconsideration and withdrawal thereof is respectfully submitted.

IV. Conclusion

In light of the foregoing amendments and remarks, applicants respectfully submit that all claims are in condition for allowance and solicit an early indication to that effect. Should Examiner Rories have any questions regarding this response, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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PENDING CLAIMS FOR USSN 08/540,343

1. (Canceled) A method of potentiating the response of a tumor cell comprising:

(a) contacting said cell with a herpesvirus; and

(b) exposing said cell to ionizing radiation.

4. (Canceled) The method according to claim 1, wherein the herpesvirus is HSV.

5. (Canceled) The method according to claim 4, wherein the HSV is HSV-1.

8. (Twice amended) The method according to claim [1] 13, wherein the tumor cell is a human tumor cell.

10. The method according to claim 8, wherein the human tumor cell is a brain cancer cell.

11. The method according to claim 8, wherein the human tumor cell is a breast cancer cell.

12. (Canceled) The method according to claim 1, wherein the cell is located within an animal, and the herpesvirus is administered to the animal in a pharmaceutically acceptable form.

13. (Amended) A method of inhibiting growth of a tumor *in vivo* comprising delivering to said tumor, in combination, a [herpesvirus] herpes simplex virus and ionizing radiation, wherein said combination is sufficient to inhibit the growth of said tumor.

14. (Canceled) The method according to claim 13, wherein the herpesvirus is HSV.

15. (Amended) The method according to claim 13, wherein the [herpesvirus] herpes simplex virus is HSV-1.

18. (Amended) A method of enhancing the effectiveness of ionizing radiotherapy comprising administering to a tumor site in a mammal (i) a pharmaceutical composition comprising a [herpesvirus] herpes simplex virus and (ii) ionizing radiation, wherein the combination of [herpesvirus] herpes simplex virus infection and radiation is more effective than ionizing radiation alone.

19. (Amended) The method according to claim 18, wherein the [administering is by means of an intravenous injection of] composition comprises from about 10^8 to about 10^{10} herpesvirus particles.

20. (Amended) The method according to claim 18, wherein the administering is by means of an oral or intravenous route.

21. (Amended) The method according to claim 18, wherein the tumor is brain tumor or breast tumor.

22. The method according to claim 18, wherein the mammal is a human.

23. (Amended) A method of killing a tumor cell comprising the steps of:

(a) contacting said tumor cell with a [herpesvirus] herpes simplex virus; and

(b) exposing said cell to a dose of ionizing radiation sufficient to kill said cell in conjunction with said [herpesvirus] herpes simplex virus.

24. (Amended) The method according to claim 23, wherein the [herpesvirus is HSV] herpes simplex virus is HSV-1.

25. (Amended) The method according to claim 13, wherein said delivering comprises injecting into a tumor site a pharmaceutical composition comprising said [herpesvirus] herpes simplex virus.

26. (Amended) The method according to claim 13, wherein the tumor is exposed to ionizing radiation selected from the group consisting of X-irradiation, γ-irradiation[, or] and β-irradiation.

27. The method according to claim 13, wherein the tumor is a brain tumor or a breast tumor.

28. (Canceled) The process according to claim 24, wherein the virus is an adenovirus.

33. (Canceled) The method according to claim 24, wherein the herpesvirus is HSV-1.

34. (Canceled) A method of potentiating the response of a tumor cell comprising:

(a) contacting said cell with an adenovirus free of an exogenous therapeutic gene; and

(b) exposing said cell to ionizing radiation.

35. (Amended) The method according to claim [34] 46, wherein the tumor cell is a human tumor cell.

36. The method according to claim 35, wherein the human tumor cell is a brain cancer cell.

37. The method according to claim 35, wherein the human tumor cell is a breast cancer cell.

38. The method according to claim 34, wherein the cell is located within an animal, and the adenovirus is administered to the animal in a pharmaceutically acceptable form.

39. The method according to claim 34, wherein the tumor is exposed to X-irradiation, γ-irradiation, or β-irradiation.

40. A method of inhibiting growth of a tumor *in vivo* comprising delivering to said tumor, in combination, an adenovirus lacking an exogenous therapeutic gene and ionizing radiation, wherein said combination is sufficient to inhibit the growth of said tumor.

41. A method of enhancing the effectiveness of ionizing radiotherapy comprising administering to a tumor site in a mammal (i) a pharmaceutical composition comprising a

adenovirus lacking an exogenous therapeutic gene and (ii) ionizing radiation, wherein the combination of adenovirus infection and radiation is more effective than ionizing radiation alone.

42. (Amended) The method according to claim 41, wherein the [administering is by means of an intravenous injection of] composition comprises from about 10^8 to about 10^{11} adenovirus particles.

43. (Amended) The method according to claim 41, wherein the tumor is exposed to ionizing radiation selected from the group consisting of X-irradiation, γ-irradiation[, or] and β-irradiation.

44. (Amended) The method according to claim 41, wherein the tumor is brain tumor or breast tumor.

45. The method according to claim 41, wherein the mammal is a human.

46. A method of killing a tumor cell comprising the steps of:

a) contacting said tumor cell with an adenovirus lacking an exogenous therapeutic gene; and

b) exposing said cell to a dose of ionizing radiation sufficient to kill said cell in conjunction with said adenovirus.

47. The method according to claim 46, wherein said delivering comprises injecting into a tumor site a pharmaceutical composition comprising said adenovirus.

48. (Amended) The method according to claim 46, wherein the tumor is exposed to ionizing radiation selected from the group consisting of X-irradiation, γ-irradiation[, or] and β-irradiation.

49. (Amended) The method according to claim 46, wherein the tumor cell is a brain tumor cell or a breast tumor cell.

50. (Amended) The method according to claim 46, wherein the [administering is by means of an intravenous injection of] composition comprises from about 10^8 to about 10^{11} adenovirus particles.

51. (New) The method of claim 40, wherein said adenovirus is Ad5.

52. (New) The method of claim 41, wherein said adenovirus is Ad5.

53. (New) The method of claim 46, wherein said adenovirus is Ad5.

54. (New) The method of claim 41, wherein said composition is administered intravenously.

55. (New) The method of claim 55, wherein said composition comprises from about 10^8 to about 10^{11} adenovirus particles.